REMARKS

I. Introduction

In response to the Office Action dated July 9, 2002, claims 1, 7, 9, 21, 46-51, 55-57 and 67 have been amended. Claims 1-10, 16-23, 33, 34 and 46-69 remain in the application. Reconsideration of the application, as amended, is respectfully requested.

II. Examiner Interview

Applicants gratefully acknowledge the comments and suggestions offered by Examiners Rawlings and Caputa during a telephonic interview held with Applicants' undersigned representative on September 16, 2003. During that interview, discussion centered on the Hoo and Wallen patents cited in the rejections under 35 U.S.C. §102 (summarized below) and amendments to the claims that would suffice to overcome these rejections. Applicants have amended the claims in accordance with this discussion with a good faith belief that these amendments and arguments are consistent with the content and spirit of the interview. Should the Examiner disagree, or otherwise find that additional issues must be addressed prior to issuing a Notice of Allowance, Applicant's representative would appreciate the courtesy of a telephone call and an opportunity to correct any deficiencies.

III. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims. These amendments to the claims are supported by the application as originally filed, and entry of these amendments is respectfully requested.

Claims 1 and 9 have been amended to clarify that the pharmaceutical composition of the invention is a vaccine, and that the stress protein complex is isolated. As indicated in the specification at page 33, lines 7-10, "isolated" means "removed from its original environment", for example, "separated from some or all of the coexisting materials in the natural system". This makes it clear that a cellular vaccine, for example, is not included within the scope of these claims.

Claim 7 has been amended to delete reference to "members of the" . . . "stress protein families", for clarity.

Claims 21 and 67 have been amended to clarify that specifying colon cancer as a particular embodiment of the type of cancer referred to in parent claims 16 and 33, respectively, is meant to convey that it is a cancer antigen that is, in this embodiment, a colon cancer antigen.

Claims 46-51 and 55-57 have been amended to correct an obvious and inadvertent typographical error in the reference to preceding claim 34.

IV. Non-Art Rejections

A. Rejection of Claim 7 Under 35 U.S.C. §112, First Paragraph

In paragraph (4) of the Office Action, claim 7 was rejected under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. The rejection is based on an allegation that the specification fails to provide an adequate description of the genus of stress family proteins to which the claim refers to meet the written description requirement of 35 U.S.C. §112, first paragraph. Applicants have amended claim 7 to delete the reference to "family of stress proteins". Although this amendment renders the rejection moot, Applicants state the following for the record.

As described in the specification at page 2, lines 12-22, the various families of stress proteins are identified in accordance with their approximate molecular weights. Further discussion of how those in the art understand the reference to stress protein families can be found in the Lee-Yoon reference (Lee-Yoon et al., 1995, J. Biol. Chem. 270:15725-15733) noted at page 54, lines 23-24 of the specification, and in Chen et al., 1996, FEBS Lett. 380:68-72, cited at page 17, lines 1-2, of the specification. Accordingly, those of ordinary skill in the art are familiar with this system of categorization and with which stress proteins belong to which family, as well as with what is meant by the indications "hsp70, hsp90, grp78 and grp94". Consideration of the references cited by the Examiner additionally confirms this familiarity within the art. For example, see: Przepiorka & Srivastava 1998 (see Table 1); Manjili et al. 2002 (see pre-filing date references cited in Part 3 therein); Li 1997 (see pages 315-316); Srivastava 1997 (see page 165); Blachere & Srivastava 1995 (see page 349); and Lee-Yoon 1995, also mentioned above (see Introduction and Discussion at pages 15725 and 15731-32). Because these proteins were well-known and well-characterized in the art prior to the filing date of the present application, those skilled in the art have no difficulty

ascertaining that Applicants had possession of the claimed invention. The written description requirement does not require applicants to disclose what is conventional or well-known to one skilled in the art.

The Examiner supports his arguments by citing *Fiers v. Revel*, 25 USPQ2d 1601 (Fed. Cir. 1993) and *Amgen, Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016 (Fed. Cir. 1991). These cases are inapplicable to the present situation because they are cases in which the claims at issue were directed to proteins and nucleic acid molecules for which the sequences had not yet been discovered. In the present case, the structure of the polypeptides encompassed by the claims is well-known in the art.

B. Rejection of Claims 16, 19, 20, 33, 34, 65 and 66 Under 35 U.S.C. §112, First Paragraph

In paragraph (5) of the Office Action, claims 16, 19, 20, 33, 34, 65 and 66 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. The rejection is based on an allegation that the specification fails to provide proper and sufficient antecedent basis to support the recitation of particular limitations and thereby violates the written description requirement of 35 U.S.C. §112, first paragraph. Applicants respectfully traverse this rejection for the following reasons.

1. Claim 16

With regard to claim 16, the rejection is based on the recitation of "wherein the immunogenic polypeptide comprises a cancer antigen." First, this limitation cannot be construed to introduce "new matter", as it is supported by the claim as originally filed. Claim 16, as originally filed, recited "an immunogenic polypeptide associated with cancer", which one skilled in the art would readily consider equivalent to "a cancer antigen". Moreover, this equivalence is expressly noted in the specification at page 26, line 9. In addition, this limitation is supported by the specification at page 25, lines 23-24, page 26, lines 10-27, and at page 41, lines 7-21.

2. Claims 19, 20, 65 and 66

Regarding claims 19, 20, 65 and 66, the rejection was based on the recitation of "extracellular domain" and "transmembrane domain" of her2/neu. These limitations are supported by the specification at page 25, line 29, and at page 63, lines 3-4. The Examiner notes that the specification appears to support recitation of more specific limitations, such as "p369" or "p546". Applicants respectfully disagree, as the specification is clear throughout that the invention is not limited to only the specific examples of immunogenic polypeptides provided, but can include any immunogenic polypeptide (see, e.g., page 19, lines 1-5, page 26, lines 10-13, and page 70, lines 1-4). Specifically with regard to her2/neu polypeptides, the specification indicates at page 25, lines 24-29, that polypeptides from the intracellular, extracellular and transmembrane domains of her2/neu were all contemplated. The recitation of exemplary amino acid sequences does not exclude other portions of the intracellular, extracellular and transmembrane domains.

Item (4) of the Advisory Action dated September 8, 2003, alleges that the disclosure does not provide a proper and sufficient basis to support the recitation of a limitation in the claims requiring the her-2/neu peptide to be derived from the extracellular domain of her-2/neu or from the transmembrane domain of her-2/neu. It is maintained that "it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads." This language suggests that the Examiner is disregarding the explicit language "extracellular domain" and "transmembrane domain", which appear, e.g., at page 63 of the specification (see lines 1-4), simply because the recitation of a subgenus is followed in parentheses by a specific embodiment falling within that subgenus. This is not the same as a case in which the subgenus was never named or implicitly described in the specification. In the present case, the subgenus is explicitly recited in the specification. Even if the Examiner insists on construing the language of the specification to explicitly recite only the single embodiments of each domain in question (which it does not), it would still be understood by one skilled in the art that Applicants were in possession of the use of an extracellular domain or transmembrane domain of her-2/neu as immunogenic polypeptides to be complexed with a stress protein.

3. Claims 33 and 34

With regard to claims 33 and 34, Applicants amended these claims exactly as suggested by the Examiner at page 4 of the prior Office Action. This added limitation, "an effective amount of the pharmaceutical composition of claim 16 to elicit an anti-tumor response in the subject", is supported by the specification at page 15, lines 15-23, and at page 48, line 16, to page 49, line 8. Accordingly, this limitation does not introduce new matter.

C. Rejection of Claims 7, 21, 46-57 and 67 Under 35 U.S.C. §112, Second Paragraph

Claim 7 was rejected because the recitation of "members of the hsp70, hsp90, grp78 and grp94 stress protein families" was regarded as rendering the claim vague and indefinite because it is unclear to which proteins the claim refers, as it is allegedly unclear which proteins are members of the hsp70, hsp90, grp78 and grp94 families. As discussed above, those skilled in the art have no difficulty ascertaining the metes and bounds of claim 7 as originally filed. To facilitate prosecution, however, Applicants have amended claim 7 to delete recitation of "family members".

Claims 21 and 67 were rejected as indefinite because the recitation of "the cancer" was regarded as lacking antecedent basis. Applicants respectfully note that the claims from which these claims depend do in fact recite "cancer". To facilitate prosecution, however, Applicants have amended claims 21 and 67 to recite "wherein the cancer antigen is a colon cancer antigen".

Claims 46-57 were rejected as indefinite because they depend from a cancelled claim. Applicants apologize for the typographical error and have amended the claims to refer to pending claim 34 instead of cancelled claim 32.

V. Prior Art Rejections

A. Rejections Under 35 U.S.C. §102

In paragraph (10) of the Office Action, claims 1, 2, 4-10, 16-18, 23, 33 and 34 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 5,891,432-A ('432). In paragraph (11) of the Office Action, claims 1-3, 5, 6, 8, 16-18 and 22 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 5,747,332-A ('332). In paragraph (12) of the Office Action, claims 1-3, 5, 6, 8 and 16-18 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S.

Patent No. 6,066,716-A ('716). Applicants respectfully traverse these rejections for the reasons provided below.

None of the references cited by the Examiner teaches a pharmaceutical vaccine composition comprising an isolated stress protein complex and a physiologically acceptable carrier, wherein the stress protein complex comprises an hsp110 polypeptide and an immunogenic polypeptide. Nor do any of these references teach that such a composition can be used for inhibiting tumor growth in a subject or for inhibiting the development of a cancer in a subject. Specifically, neither the '332 patent nor the '716 patent teaches a vaccine comprising an hsp110 polypeptide. While the '432 patent discloses the use of any of a variety of immunomodulatory molecules in cellular vaccines, this disclosure does not anticipate claims relating to isolated stress protein complexes.

Moreoever, to the extent that some earlier-filed patent specifications disclose the use of a heat shock protein in combination with an immunogenic polypeptide, these references do not teach that hsp110 has therapeutic properties. Although hsp110 is mentioned as an example of a heat shock protein, no basis for expecting the structurally dissimilar hsp110 to have the same immunogenic utility as, for example hsp70, is provided. Because one of ordinary skill in the art would not have had a reasonable expectation of success with a pharmaceutical vaccine composition comprising isolated hsp110 complexed with an immunogenic polypeptide in the absence of data demonstrating the ability to elicit an effective immune response, none of the cited references discloses the claimed invention, and none provides an enabling disclosure (see MPEP §2121).

Applicants' specification discusses at page 2, lines 23-30, the lack of information available about the function and activity of the larger stress proteins, hsp110 and grp170. This paragraph also points out the divergence of these larger stress proteins from the more extensively studied hsp70 in sequence as well as size. Moreover, the existence of hsp110 in parallel with hsp70 in the cytoplasm, and likewise of grp170 with grp78 in the endoplasmic reticulum is further suggestive of divergent functions. As stated in Applicants' specification at page 3, lines 1-2, "[n]ot all stress proteins function as vaccines, however, and it can be expected that different ones may exhibit different activities." This statement that one cannot presume all stress proteins function as vaccines is supported by the specification's disclosure at page 48, lines 7-10, that grp78 failed to exhibit the same immunogenic properties as shown by the other stress proteins studied in this example.

Accordingly, the mere fact that hsp110 had been identified as a stress protein was not enough to indicate that it could be used to inhibit cancer or other disease.

1. *U.S. Patent 5,891,432 to Hoo ('432)*

The '432 patent teaches a cellular vaccine having a membrane-bound fusion protein that includes a non-antibody immunomodulatory molecule fused to a heterologous membrane-attachment domain and further including a disease-associated antigen. Although the specification teaches, and the claims are directed to, use of GM-CSF as the non-antibody immunomodulatory molecule, the specification also mentions heat shock proteins as an example of a non-antibody immunomodulatory molecule. The paragraph bridging columns 6-7 of '432 lists the various identified families of heat shock proteins: HSP110, HSP90, HSP70, HSP60, HSP25, HSP20 and HSP8.5, and then goes on to note that HSP60, HSP70 and HSP90 are expressed on the cell surface of mycobacteria-infected, HIV-infected, or tumor cells, and that HSP65 is an example of an immunomodulatory molecule useful in the vaccines of the invention. References are cited to support the statements regarding these features of HSP60, HSP70, HSP90 and HSP65. No representation is made, however, that HSP110 shares these same features with HSP60, HSP70, HSP90 and HSP65 or that HSP110 itself would be useful in a vaccine. Moreover, the '432 patent does not teach or suggest the use of an isolated stress protein complex comprising hsp110 and an immunogenic polypeptide.

Accordingly, the '432 patent does not teach each element of Applicants' claims, and withdrawal of the rejection based on '432 is respectfully requested.

2. *U.S. Patent 5,747,332 to Wallen ('332)*

The '332 patent teaches a method for purifying heat shock proteins. The specification of this patent includes a list of known heat shock proteins, including members of the hsp60 family, the hsp70 family, the hsp90 family and hsp104-105 family, of which hsp110 is identified as a member. The Background portion of this patent, at column 1, lines 39-50, mentions that a number of different heat shock proteins have been shown to exhibit immunogenicity, including gp96, hsp90,

and hsp70. The '332 patent does not teach that hsp110 is immunogenic nor does it teach or suggest a vaccine comprising hsp110 complexed with an immunogenic polypeptide.

Accordingly, the '332 patent does not teach each element of Applicants' claims, and withdrawal of the rejection based on '332 is respectfully requested.

3. *U.S. Patent 6,066,716 to Wallen ('716)*

The '716 patent is a divisional of the '332 patent, and its disclosure is the same as that for the '332 patent. Like the '332 patent, '716 does not teach that hsp110 is immunogenic nor does it teach or suggest a vaccine comprising hsp110 complexed with an immunogenic polypeptide. Accordingly, the '716 patent does not teach each element of Applicants' claims, and withdrawal of the rejection based on '716 is respectfully requested.

B. Rejections Under 35 U.S.C. §103

In paragraph (14) of the Office Action, claims 1-10, 16-18, 22, 23, 33 and 34 were rejected under 35 U.S.C. §103(a) as allegedly obvious in view of the combination of U.S. Patent Nos. 5,747,332-A ('332), 5,981,706-A ('706), and 6,066,716-A ('716), in view of Disis et al. (Clinical Cancer Research 5:1289-1297, 1999), and further in view of U.S. Patent No. 6,322,790-B1 ('790), and in still further view of U.S. Patent Nos. 5,891,432-A ('432), 6,331,299-B1 ('299), and Lee-Yoon et al. (Journal of Biological Chemistry 270:15725-15733). Applicants respectfully traverse the rejection of these claims for the reasons provided below.

The teachings of '332, '716 and '432 as discussed above, are limited to mentioning the immunogenic properties of some heat shock proteins, namely hsp70, hsp90 and gp96, and the identification that hsp110 is also a heat shock protein. These references do not teach that hsp110 is immunogenic or otherwise useful as a vaccine in the inhibition of cancer. Prior to Applicants' invention, it was not known that hsp110 has immunogenic properties and is suitable for use as a vaccine (see publication by the inventors: Wang et al., 2001, J. Immunology 165:490-497). The 5 additional references on which the rejection under 35 U.S.C. §103 is based are discussed below.

1. U.S. Patent 5,981,706 to Wallen ('706)

The '706 is a continuation-in-part of the '332 patent, and its disclosure includes that for the '332 patent plus adds a number of specific examples of peptides for use in ADP-heat shock protein-peptide complexes. Like the '332 patent, '706 does not teach that hsp110 is immunogenic or otherwise suitable for use as a vaccine. It does not teach or suggest the use of hsp110 to inhibit cancer or to elicit an immune response.

2. Disis et al., Clinical Cancer Research 5:1289-1297, 1999 (Disis)

Disis teaches that immunity to the her2/neu oncogenic protein can be generated in patients with breast or ovarian cancer using peptides derived from the her2/neu protein. It does not teach or suggest combining an immunogenic her2/neu peptide with hsp110. It does not teach or suggest the use of hsp110 to inhibit cancer.

3. U.S. Patent 6,322,790 to Srivastava ('790)

The '790 patent teaches stress proteins complexed with peptides and their use for eliciting an immune response. It mentions hsp70, hsp90 and gp96 as examples of stress proteins that have demonstrated ability to elicit an immune response (column 3, lines 23-51). It does not teach or suggest the use of hsp110 to inhibit cancer or to elicit an immune response.

4. U.S. Patent 6,331,299 to Rothman ('299)

The '299 patent teaches use of polynucleotides encoding a heat shock protein to elicit an immune response. It does not teach or suggest the use of hsp110 to inhibit cancer or to elicit an immune response.

5. Lee-Yoon et al., J. Biol. Chem. 270:15725-15733, 1995 (Lee-Yoon)

Lee-Yoon teaches that the amino acid sequence for hamster hsp110 shares about 30-33% identity with members of the hsp70 family, and that hsp110 is a large and highly unusual heat shock protein that diverges considerably from the hsp70 family. At page 15732, Lee-Yoon discusses the potential functions of hsp110 based on the deduced amino acid sequence of this protein, notes that

it differs significantly from hsp70 (e.g., does not migrate from the cytoplasm into the nucleolus of heat-shocked cells as does hsp70) and concludes that hsp110 may be expected to show both similarities and differences in function with respect to the more extensively studied hsp70. It does not teach or suggest the use of hsp110 to inhibit cancer or to elicit an immune response.

6. The 8 References Do Not Teach or Suggest the Claimed Invention

Because none of the 8 references cited in the Office Action, taken alone or in combination, teaches that hsp110 is capable of eliciting an immune response, these references cannot teach or suggest a pharmaceutical vaccine composition comprising an isolated stress protein complex comprising hsp110 and an immunogenic polypeptide nor can they teach or suggest use of such a composition for inhibiting cancer or tumor growth. Even when combined, the references teach away from Applicants' invention. For example, the combined references would teach use of a pharmaceutical composition comprising a heat shock protein selected from hsp70, hsp90 or gp96, and would lead the skilled artisan away from the use of hsp110.

C. Response to Arguments

1. The Wallen Patents Do Not Teach or Suggest an HSP110 Vaccine

The assertion at pages 9 and 10 of the Office Action, alleging that U.S. Patent Nos. 5,747,332 and 6,66,716 (both issued to Wallen) teach a "pharmaceutical composition that can be administered to a subject in an effective amount to treat or prevent cancer in the subject, wherein said composition comprises heat shock protein complexes comprising hsp110 associated by a non-covalent interaction with an immunogenic polypeptide" is erroneous. The Wallen patents teach a method for purifying heat shock proteins, and they disclose that hsp110 is one example of a heat shock protein. These references do not teach a pharmaceutical or vaccine composition for treatment or prevention of cancer, nor do they teach the use of hsp110 for treatment or prevention of cancer, nor do they teach that hsp110 is immunogenic. Instead, the Wallen patents explicitly identify three other heat shock proteins as immunogenic, but not hsp110. By inference, Wallen teaches away from the selection of hsp110 for use in a cancer vaccine.

Moreover, the Wallen patents teach the purification of heat shock proteins through complexing with ADP. Because hsp110 does not bind ATP or ADP (see Chen et al., 1996, FEBS Letters 380:68-72, of record and cited in specification at page 17, lines 1-2), hsp110 could not be used or isolated as a complex with ADP in the manner taught in the Wallen patents. Accordingly, all of the Wallen patents teach away from the use of hsp110.

2. *The Combined References Do Not Suggest An HSP110-Her-2/neu Vaccine*

At pages 11-12 of the Office Action, it is alleged that the combination of references identified above would have rendered obvious the production of a pharmaceutical composition comprising hsp110 and a peptide derived from the intracellular domain of her2/neu. It is further alleged that one of ordinary skill in the art would have been motivated to produce a pharmaceutical composition comprising a polynucleotide sequence encoding a fusion protein comprising hsp110 and an immunogenic peptide derived from the intracellular domain of her2/neu because there had been a long-felt need for a more effective method for treating and preventing cancers, such as breast and ovarian cancer, that overexpress the her2/neu oncogenic protein. Yet the Examiner has pointed to no teaching or suggestion that would motivate one to select the structurally dissimilar and uncharacterized hsp110 over the well-characterized hsp70. The Examiner's reasoning points only to a motivation to combine a her2/neu domain with a heat shock protein, and assumes that any heat shock protein would be selected, regardless of whether it was structurally and functionally suitable for use in a therapeutic context.

3. *Not All Stress Proteins Are Vaccines*

Some stress proteins have been shown to serve as chaperones. As of the priority date of the present application, other stress proteins had been identified, but their ability to chaperone other proteins was unknown. It is not known why some stress proteins function as chaperones and others do not. Those skilled in the art would have held doubts as to whether additional stress proteins, particularly uncharacterized ones known to have considerably divergent structure and function, would share the same immunogenic properties of the well-studied hsp70.

Applicants have demonstrated that two of the three stress proteins described in their examples (hsp110 and grp170, but not grp78) do in fact exhibit remarkable and effective immunogenic properties and function effectively as vaccines for the treatment and prevention of cancer. The discovery that hsp110 and grp170 are even better chaperones than hsp70 was surprising and unexpected given the divergence in size and sequence between hsp70 and these larger stress proteins. As noted at page 16, lines 16-17 and 23-24, of the specification, hsp110 is more than just another alternative to hsp70. Rather, hsp110 is capable of binding much larger polypeptides than can hsp70, and binds with greater efficiency, which is particularly surprising given the extent to which it diverges from the structure and function of hsp70.

VI. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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